



BARDA's Broad Spectrum Antimicrobial (BSA) Program

Joe Larsen, Ph.D.
Acting Deputy Director
BARDA Division of CBRN Medical Countermeasures

NVAC Briefing
February 2015



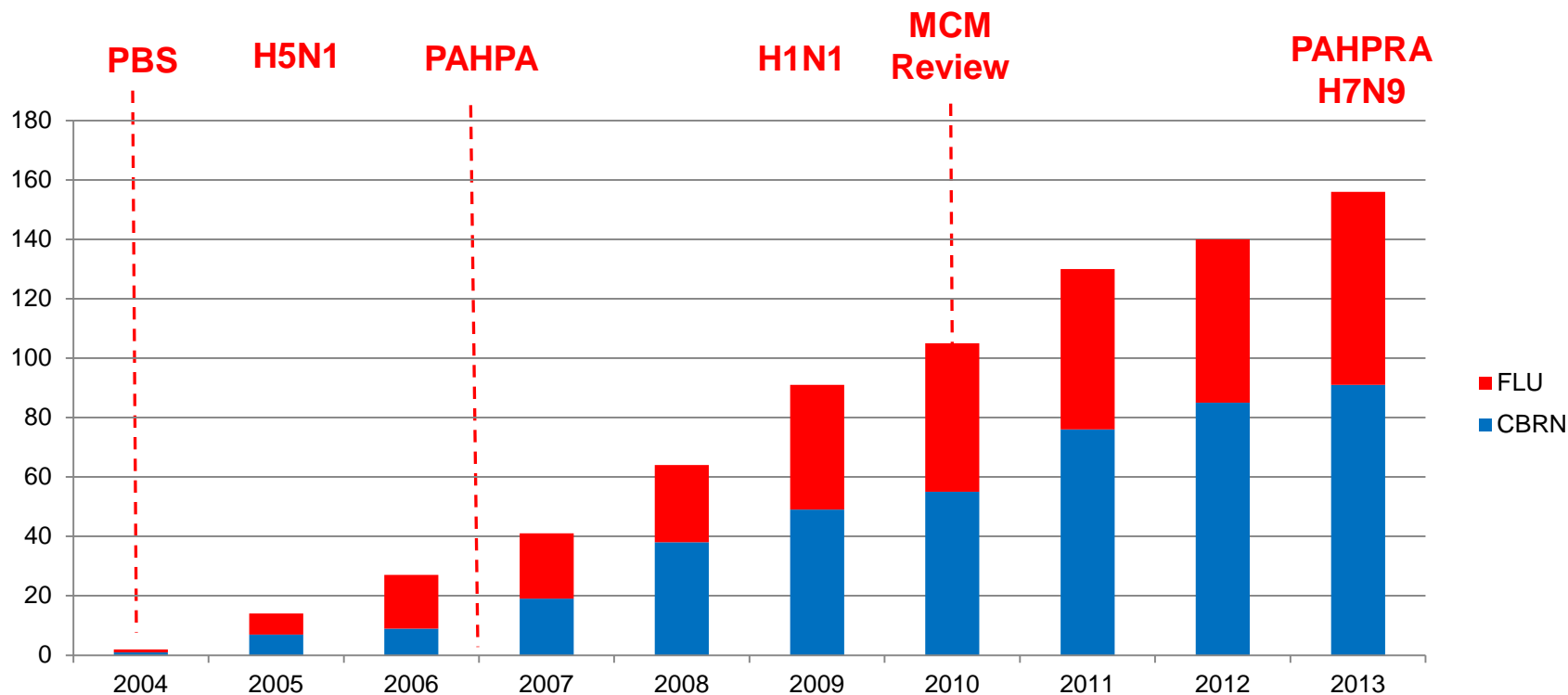
BARDA Principles at Work



- **Exists to address the medical consequences of biothreats, pandemic influenza and emerging infectious diseases, including antimicrobial resistance.**
- **Works with our federal partners to transition medical countermeasures from early development into advanced development towards ultimate FDA approval.**
- **Has established public-private partnerships with industry; sharing in development costs.**
- **Established a network of core services to assist developers in non-clinical, clinical, manufacturing, and fill/finish activities.**
- **Provides subject matter expertise in all aspects of product development.**
- **Make sure that safe and effective products are available if needed during an incident or public health emergency.**

BARDA Created a Robust & Productive MCM Development Pipeline

- More than 150 MCM product candidates in development since 2004 (aggregate)

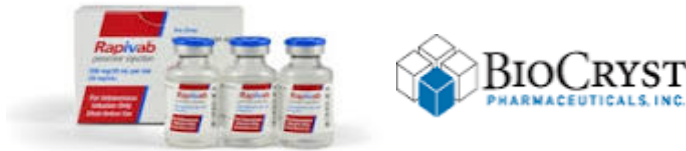


BARDA's MCMs Have Been Approved by the FDA

Cell-based Influenza Vaccine



Influenza IV Antiviral Drug



H1N1 & H5N1 Vaccine w/ Adjuvant



GlaxoSmithKline

Next-Gen Portable Ventilators

Covidien



Recombinant-based Influenza Vaccine



Protein Sciences Corp.

Anthrax Antitoxin



HGS/GSK

Botulinum Antitoxin



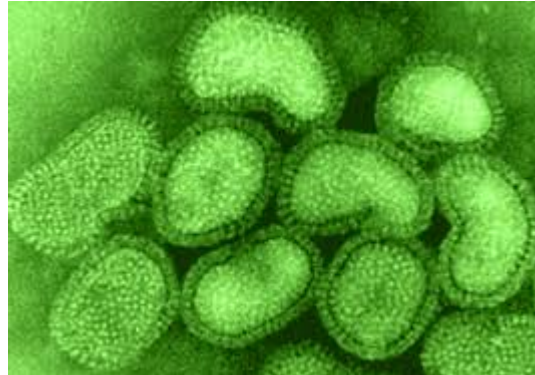
Cangene

Flu/RSV POC Diagnostic

3M/Focus



The BARDA Model



- The BARDA model works to address products for which there is no, to a limited, commercial market
 - Products FDA approved/cleared for biothreats and pandemic influenza
 - Products stockpiled for potential use during a declared emergency
- This model is being successfully applied to antimicrobial resistance
 - Utilization of novel public:private partnerships to incentivize antibiotic research and development
 - 4 products in Phase III clinical development
 - 2 products have hit endpoints in Phase III trials



BSA Program Objective



To help revitalize the antimicrobial pipeline by forming innovative public-private partnerships with companies engaged in antimicrobial therapy development

BARDA's BSA Supported Product Pipeline

Sponsor	Compound	Development			
		Preclinical	Phase I	Phase II	Phase III
Antibiotics	Achaogen	Next-generation aminoglycoside: Broad Spectrum plague, tularemia and carbapenem resistant Enterobacteriaceae (CRE)			
	CUBRC/ Tetrphase	A novel fully synthetic tetracycline: Broad Spectrum plague, tularemia, complicated intra-abdominal and urinary tract infections (cIAI, cUTI)			
	Cempra	Next-generation fluoroketolide: Broad Spectrum anthrax, tularemia, gonorrhea and community-acquired bacterial pneumonia (CABP)			
	Basilea	A novel surfactant: Broad Spectrum MDR Gram negative infections, melioidosis, glanders			
	Rempex	Carbapenem/ β -lactamase inhibitor: Broad Spectrum CRE, cUTI, hospital-acquired pneumonia/ventilator-associated pneumonia (HAP)/(VAP), melioidosis, glanders			
	GSK	Broad Spectrum Antibiotic Portfolio A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development			

Disclaimer: The above projects are supported by BARDA's BSA Program utilizing non-dilutive funding via a contract and/or agreement. The stage of development is approximate as of July 2014 (please refer to the sponsors site for updated information). The table represents the compounds most advanced commercial indication being pursued by the developer.



BARDA's Portfolio Partnership for Antibacterial Drug Development



GlaxoSmithKline



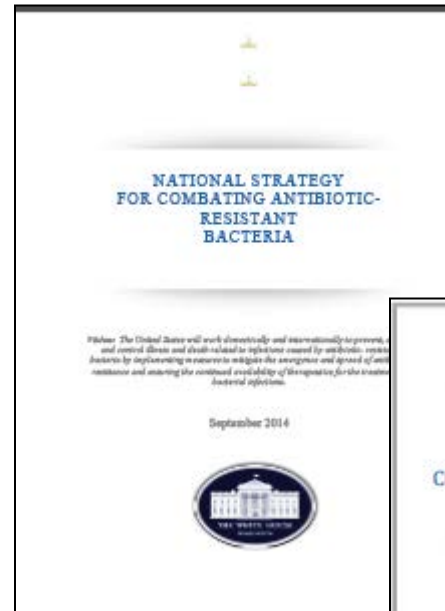
- Established 5 year \$200M public:private partnership in May 2013
- HHS's first use of Other Transactional Authority – provided under the Pandemic and All-Hazards Preparedness Act (2006)
- Supports the development of multiple antibiotic candidates
- Allows for activities and resources to be adjusted fluidly to adapt to technical risk and programmatic priorities
- Governance is through a BARDA:GSK Joint Oversight Committee
- Results to date:
 - Progressed one candidate to Phase II clinical development
 - Selecting lead clinical candidate for novel Gram negative target this month



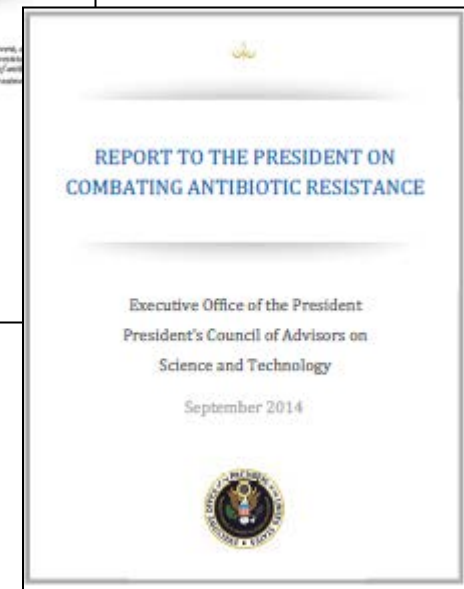
White House Initiative on AMR



CARB Working Groups



PCAST



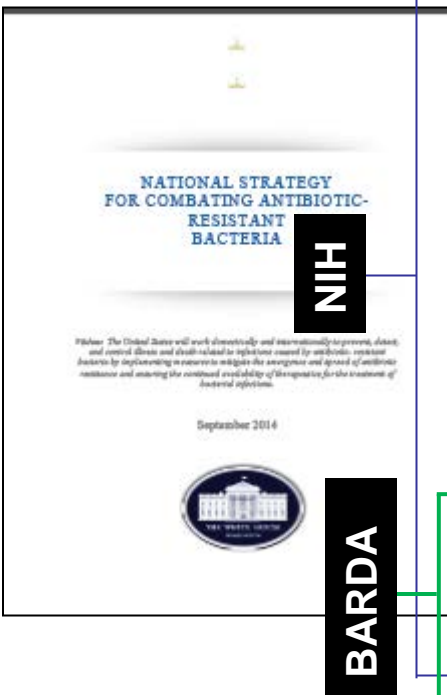
Executive Order -- Combating Antibiotic-Resistant Bacteria

EXECUTIVE ORDER

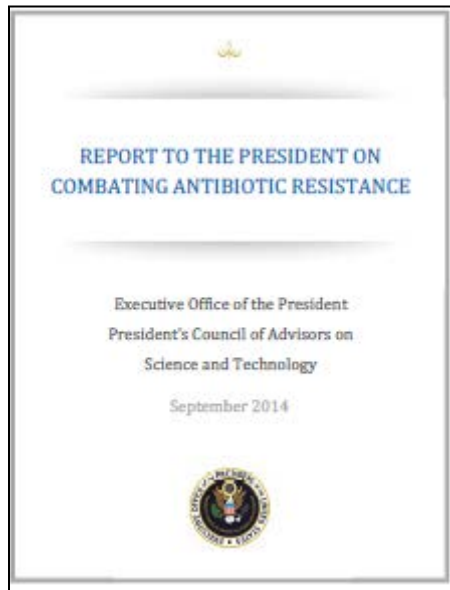
National Strategy

- GOAL 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines

- 4.1 Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic resistance and the spread of resistance genes that are common to animals and humans.
- 4.2 Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.
- 4.3 Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.
- 4.4 Develop non-traditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.
- 4.5 Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.
- 4.6 Enhance opportunities for public-private partnerships to accelerate research on new antibiotics and other tools to combat resistant bacteria.
- 4.7 Create a biopharmaceutical incubator—a consortium of academic, biotechnology and pharmaceutical industry partners—to promote innovation and increase the number of antibiotics in the drug-development pipeline.



PCAST Recommendations



5.2 'Push' mechanisms: Direct Federal partnership in antibiotic development

- Recommended additional support for subsidizing research and development costs

5.3 'Pull' mechanisms: Economic rewards for drug developers

- Substantially higher reimbursement for antibiotics
- De-linkage models
- Tradable voucher to extend patent life
- Antibiotic usage fee

CARB Working Group on Economic Incentives

- Currently evaluating PCAST proposed incentives



BARDA Receives Expanded Authority

ASPR
ASSISTANT SECRETARY FOR
PREPAREDNESS AND RESPONSE

Executive Order -- Combating Antibiotic-Resistant Bacteria

EXECUTIVE ORDER

Sec. 8. Promoting New and Next Generation Antibiotics and Diagnostics. (a) As part of the Action Plan, the Task Force shall describe steps that agencies can take to encourage the development of new and next-generation antibacterial drugs, diagnostics, vaccines, and novel therapeutics for both the public and agricultural sectors, including steps to develop infrastructure for clinical trials and options for attracting greater private investment in the development of new antibiotics and rapid point-of-care diagnostics. Task Force agency efforts shall focus on addressing areas of unmet medical need for individuals, including those antibiotic-resistant bacteria CDC has identified as public and agricultural health threats.

(b) Together with the countermeasures it develops for biodefense threats, the Biomedical Advanced Research Development

Authority in HHS shall develop new and next-generation countermeasures that target antibiotic-resistant bacteria that present a serious or urgent threat to public health.

(c) The Public Health Emergency Medical Countermeasures Enterprise in HHS shall, as appropriate, coordinate with Task Force agencies' efforts to promote new and next-generation countermeasures to target antibiotic-resistant bacteria that present a serious or urgent threat to public health.



BARDA's Antimicrobial Program



- Historically, BARDA's program had focused on products (antibiotics) that had spectrums that covered both biothreat and public health pathogens
- With the CARB Executive Order, our mission scope has been broadened to allow programs that focus explicitly on public health pathogens that are antimicrobial resistant
 - Focus on the CDC pathogen of Urgent or Serious Public Health Concern
- Vaccines for AMR pathogens may play a role in our broadened mission space

BARDA's Mandate for AMR

Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*



Examples of AMR Vaccines in Phase I-III Development



ACAM-Cdiff (<i>Clostridium difficile</i> toxoid vaccine)	Sanofi Pasteur Swiftwater, PA	<i>Clostridium difficile</i> infection (prevention) (Fast Track)	Phase III www.sanofi.com
IC84 (recombinant fusion protein vaccine)	Novartis Vaccines Cambridge, MA Valneva Vienna, Austria	<i>Clostridium difficile</i> infection (prevention)	Phase I www.novartisvaccines.com
PF-06425090 (<i>Clostridium difficile</i> vaccine)	Pfizer New York, NY	<i>Clostridium difficile</i> colitis	Phase I www.pfizer.com
PF-06290510 (4-antigen <i>Staphylococcus aureus</i> vaccine, SA4g)	Pfizer New York, NY	staphylococcal infection	Phase II www.pfizer.com
<i>Staphylococcus aureus</i> recombinant conjugated vaccine	GlaxoSmithKline Research Triangle Park, NC	<i>Staphylococcus aureus</i> infection (prevention)	Phase I www.gsk.com
<i>Staphylococcus aureus</i> vaccine	Novartis Vaccines Cambridge, MA	staphylococcal infection	Phase I www.novartisvaccines.com

Adapted from PhRMA 2013 Report on Infectious Disease
Biopharmaceutical Research



Discussion Points



- Vaccines were not heavily discussed in either the PCAST report or CARB National Strategy.
 - Should vaccines be a component of the overall USG strategy to combat AMR?
 - Should BARDA include vaccines as a component of its antimicrobial program?
- If so, where are the greatest areas of impact? Where should the focus be?